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| EXAMINER |
|---|
| VANDERVEGT, FRANCOIS P |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/757,716 | MAGNA ET AL. | |
| | Examiner | Art Unit | |
| | F. Pierre VanderVegt | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *45-49,51,53-62 and 65-68* is/are pending in the application.

4a) Of the above claim(s) *45,47,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,48,49,51,53-60 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *01092001*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

This application is a continuation of U.S. Application Serial Number 09/153,586, which claims the benefit of the filing date of provisional applications 60/064,552 and 60/046,555.

Claims 1-44, 50, 52, 63 and 64 have been canceled.

Claims 45, 61 and 63 stand as withdrawn pursuant to Applicant's election with traverse in the paper filed June 23, 2002.

Claims 45-49, 51, 53-62 and 65-68 are currently pending.

Claims 45, 47, 61 and 62 stand as withdrawn pursuant to Applicant's election with traverse in the paper filed June 23, 2002.

Claims 46, 48, 49, 51, 53-60 and 65-68 are the subject of examination in the present Office Action.

### *Response to Arguments*

1. In view of the Appeal Brief filed on August 28, 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2 In view of the new grounds of rejection presented below, the present Office Action is made **NON-FINAL**.

## *Specification*

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the specification as originally filed does not provide support for the recitation of "a polypeptide having a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" in claim 46.

## *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 46, 48, 49, 51, 53-60 and 65-68 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible asserted utility or a well-established utility.

The claims are most broadly drawn to a antibodies directed to "a) a polypeptide having the amino acid sequence of SEQ ID NO: 1, b) a polypeptide having a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity, c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity, and d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." Claims are also drawn to the making of antibodies using the sequences [claims 53 and 56] and methods of diagnosis using the antibodies [claim 47].

The polypeptide of SEQ ID NO: 1 and naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 to which the claimed antibodies are directed are not supported by either a specific and substantial asserted utility or a well-established utility. While the specification asserts that the utility of the polypeptides is for "the diagnosis, prevention and treatment of arthropathies, immunological disorders and cancers" (page 3, lines 10-13 for example), in order to establish such an asserted utility as substantial or well-established, there must be credible evidence that the polypeptide is of consequence in the conditions being diagnosed or treated. A well established utility is a specific, substantial, and credible utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. Identifying a DNA segment derived from overlapping cDNAs and determining a function for it's deduced putative polypeptide product based solely on primary polypeptide sequence does not endow the polypeptide with such a utility. Applicant has generated the deduced amino acid sequence of the protein product (SEQ ID NO:1) from a consensus

nucleic acid sequence generated via computer alignments using the partial cDNA sequence of Masuda et al (8 on form PTO-1449) and a computer homology search of cDNAs from an osteoarthritic chondrocyte cDNA library. SEQ ID NO: 1 was derived from cDNA sequences of three clones from the same cDNA library (page 15, line 26 to page 16, line 10 of the instant specification, for example). Applicant has disclosed this deduced amino acid sequence is a nucleotide pyrophosphohydrolase protein termed by Applicant as NTPPH-2 and has disclosed that this computer generated molecule polypeptide has 50% amino acid identity in a computer generated sequence alignment with the known porcine nucleotide pyrophosphohydrolase disclosed by Masuda et al (8 on form PTO-1449) and Cardenal et al (7 on form PTO-1449) as NTPPH; instantly referred to by the specification as NTPPH-1 (page 2, lines 16 to page 3, line 9 and page 16, lines 16-17 for example). The specification states purported uses for the protein including "the diagnosis, prevention and treatment of arthropathies, immunological disorders and cancers" (page 3, lines 10-13 for example). However, there is no clear guidance from the specification that their protein would have the same or similar biological properties as NTPPH because the proposed uses for the claimed computer deduced protein are based solely upon computer alignment with known proteins and the site of isolation, osteoarthritic chondrocytes, of the cDNA sequences from which the amino acid sequence was deduced. Since the claimed protein and the prior art proteins only share 50% sequence identity there would be no predictability that this small sequence identity would render the biological activities of the proposed protein and the known porcine nucleotide pyrophosphohydrolase similar because Applicant has not disclosed whether the biological activity of both proteins resides within the common region(s) or elsewhere within the sequence of the proteins, nor does the specification indicate whether the proteins share conserved active or binding sites. Brenner et al. (Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; U1 on form PTO-892), at page 6076, column 2, states that, "Fig. 2 shows one of the many pairs of proteins with very different structures that nonetheless have high levels of identity over considerable aligned regions. Despite the high identity, the raw and the statistical scores for such incorrect matches are typically not significant. The principal reasons percentage identity does so poorly seems to be that it ignores information about gaps and about the conservative or radical nature of residue substitutions. From the PDB90D-B analysis in Fig. 3, we learn that 30% identity is a reliable threshold for this database only for sequence alignments of at least 150 residues." Brenner therefore shows in Fig. 2 that reliance upon high identity alone in many pair wise comparisons is insufficient to relate information about structural and/or functional relatedness and in the analysis of Fig. 3 indicates that information which can be gleaned from sequence identity comparisons is database-specific, not general. The Brenner reference puts further emphasis on the need for structural relationships on page 6074, end of first column in the statement, "Since the discovery that the structures of hemoglobin and myoglobin are very similar though their sequences are not, it has been apparent that comparing structures is a more powerful (if less

convenient) way to recognize distant evolutionary relationships than comparing sequences." Therefore, the Brenner reference teaches that sequence identity alone is insufficient to establish functional relationships between proteins, rather it must be used in concert with structural information to accurately establish relationships between proteins. The instant specification does not provide any information on the structural characteristics of NTPPH-2, only an assertion of 3 putative N-glycosylation sites and 25 putative phosphorylation sites and that "NTPPH-2 has chemical and structural homology with NTPPH-1" (page 16, lines 11-17 for example), but this "structural homology" is based solely on the finding of 50% homology to NTPPH, and not actual structural determination. According to Brenner, sequence homology must be used in concert with structural information, rather than using one to guess the other. The instant specification does not provide any information about the structure of the predicted NTPPH-2 polypeptide, only sequence identity to the porcine nucleotide pyrophosphohydrolase NTPPH, and for this reason the specification provides insufficient information to enable the artisan to reasonably predict that NTPPH-2 is functionally related to NTPPH and therefore the specification does not teach the artisan a credible utility for NTPPH-2.

Because the characteristics of NTPPH-2 are based solely upon sequence identity of the protein with other previously known proteins and not based upon analysis of any actually-produced protein product, no biological activity has been established for NTPPH-2. As such, further research would be required to identify or reasonably confirm a "real world" context of use, for example, to identify any function of NTPPH-2 and conditions for which NTPPH-2 polypeptides, fragments and "naturally occurring" 90% identical polypeptides would be of diagnostic or therapeutic significance. Accordingly, without a "real-world" use for the protein, antibodies specific therefore are equally not useful, as basic research such as studying the properties of the product of the polypeptide are not considered substantial and credible utility for the claimed invention. Therefore, the specification does not fairly disclose a substantial and credible utility for the antibody of the instant claims. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 46, 48, 49, 51, 53-60 and 65-68 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Additionally, even in view of a testable activity for those polypeptides that are "naturally-occurring" variants of SEQ ID NO:1 comprising at least 90% identity over the full length of SEQ ID NO:3, the specification still does not appear to provide sufficient guidance such that the skilled artisan is enabled to make and use an antibody to those polypeptides commensurate in scope with the instant claims.

The specification discloses a single working example of a polypeptide that is naturally-occurring and has at least 90% identity to SEQ ID NO: 1; namely, the polypeptide of SEQ ID NO: 1. Nevertheless, there is insufficient guidance in the specification as-filed to direct a person of skill in the art as to how to make and use antibodies to a polypeptide comprising a "naturally-occurring" amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 even wherein said naturally-occurring amino acid sequence has nucleotide pyrophosphohydrolase activity.

Applicant does not appear to have provided sufficient guidance with respect to "naturally-occurring" polypeptides and how to make and use antibodies to them. Although the specification does provide some general guidance as to how to isolate other nucleic acids related to the nucleic acid encoding SEQ ID NO: 1 and then test those polypeptides encoded by the related nucleic acids for nucleotide pyrophosphohydrolase function (e.g., page 55), it is unpredictable that other "naturally-occurring" polypeptides having nucleotide pyrophosphohydrolase activity and at least 90% amino acid sequence identity to SEQ ID NO: 1 exist.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Applicant does not appear to provide sufficient guidance as to other sources of "naturally-occurring" polypeptides which are at least 90% identical to SEQ ID NO: 1 and have nucleotide pyrophosphohydrolase activity. The state of the art did not recognize other "naturally-occurring" polypeptides that had nucleotide pyrophosphohydrolase activity and were at least 90% identical to SEQ ID NO: 1. Even though the level of skill in the art for isolating "naturally-occurring" polypeptides encoded by nucleic acids related to the nucleic acid encoding SEQ ID NO: 1 may have been high with respect to the techniques employed, skill in the art does not render the existence of a "naturally-occurring" polypeptide predictable.

The presence of a single working example and the failure of the state of the art either at the time of filing or since to recognize other "naturally-occurring" polypeptides at least 90% identical to SEQ ID NO: 1 and having nucleotide pyrophosphohydrolase activity indicates that it was highly unpredictable that additional polypeptides meeting these limitation could be isolated, particularly based on the limited guidance provided in the specification as filed. Unlike the fact pattern of In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) where the presence of a hybridoma producing an antibody having the desired properties among the many hybridomas was predictable, in the instant case it is not predictable that other "naturally-occurring" polypeptides exist. Therefore, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue with respect to other "naturally-occurring" polypeptides other than SEQ ID NO: 1.

Consequently, a person of skill in the art is not enabled to make and use an antibody to a "naturally-occurring" polypeptide at least 90% identical to SEQ ID NO: 1 and having nucleotide pyrophosphohydrolase activity; as encompassed by the full breadth of the claims as currently recited, irrespective of the particular form of the antibody (polyclonal, monoclonal, etc.).

6. Claims 46, 48, 49, 51, 53-60 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite as part of the invention an antibody which specifically binds a polypeptide comprising a "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1" wherein said naturally-occurring amino acid sequence has nucleotide pyrophosphohydrolase activity.

A polypeptide comprising the amino acid sequence of SEQ ID NO:1 is adequately described in the specification as-filed, thereby providing an adequate written description of an antibody which specifically binds the polypeptide of SEQ ID NO:1 or immunogenic fragments thereof.

A polypeptide comprising a "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" wherein said naturally-occurring amino acid sequence has nucleotide pyrophosphohydrolase activity is a recitation of a genus of polypeptides for which Applicant has disclosed a single species: the polypeptide of SEQ ID NO:1. The claim recites that the polypeptide to which the antibody binds is "naturally-occurring" and has a testable function of "nucleotide pyrophosphohydrolase activity." The specification proposes that other members of the "naturally-occurring" polypeptide genus may be identified by using hybridization probes to identify DNAs or RNAs

related to the nucleic acid encoding SEQ ID NO:1, expressing the polypeptide, and assaying the polypeptide for nucleotide pyrophosphohydrolase activity (see page 39 and page 55 in particular).

However, Applicant does not appear to have provided a description of which polypeptide sequences are "naturally-occurring", even among those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO: 1. Neither does Applicant appear to have provided a description of how the structure of the polypeptide of SEQ ID NO:3 relates to the structure of other "naturally-occuring" polypeptides which have nucleotide pyrophosphohydrolase activity, even for those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO: 1. Thus neither the common attributes of the genus nor the identifying attributes of individual species other than SEQ ID NO: 1 appear to have been described.

One of skill in the art would conclude that Applicant was not in possession of the claimed genus of polypeptides comprising a "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" wherein said naturally-occurring amino acid sequence has nucleotide pyrophosphohydrolase activity. Since Applicant does not appear to have been in possession of the genus of polypeptides to which the instantly recited antibody specifically binds; Applicant in turn does not appear to be in possession of the genus of antibodies specifically binding these polypeptides.

Therefore, only an antibody to SEQ ID NO: 1 or immunogenic fragments thereof meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 46, 49, 51, 53, 54, 55, 59, 60, and 65-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Cardenal et al. (Arthr. Rheum. [1996] 39(2):245-251; 7 on form PTO-1449).

Cardenal teaches a polyclonal antibody preparation to porcine NTPPH (page 246 in particular), a protein disclosed by the instant specification as NTPPH or NTPPH-1 (SEQ ID NO: 3; page 2, line 16 to page 3, line 13 and Figure 2 of the instant specification, for example) and as being 50% identical to the NTPPH-2 of instant SEQ ID NO: 1. It is noted from the sequence alignment of Figure 3, that SEQ ID NO: 1 "has" a number of sequences in common with NTPPH taught by Cardenal. Accordingly, a preparation of polyclonal antibodies to the NTPPH protein of Cardenal would contain antibodies that are reactive with SEQ ID NO: 1 [claims 46, 49, 54-55, 59, 60 and 65-68]. Cardenal teaches detection of the polyclonal antibody precipitated NTPPH protein using a composition comprising a label (Figure 2 in particular)[claim 51]. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). The method of claim 53 is included because in the phrase "having an amino acid sequence of SEQ ID NO: 1, or an immunogenic fragment thereof" the recitation of "having" is considered open (*i.e.*, comprising) opens the claim up to include unrecited elements even in large amounts, consistent with the recitation of "comprising." Claims 59-60 are included because the claims are drawn to a composition but are drafted in a product-by-process manner and the antibodies remain the same irrespective of the screening method. The prior art teaching anticipates the claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 46, 48 and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cardenal et al. (Arthr. Rheum. [1996] 39(2):245-251; 7 on form PTO-1449) in view of Harlow et al (V1 on form PTO-892).

Cardenal has been discussed supra.

Cardenal does not teach monoclonal antibodies.

Harlow teaches that any substance which can elicit a humoral response can be used to prepare mAbs and that mAbs are powerful reagents for the testing for the presence of a desired epitope. Harlow teaches methods for immunizing animals for the production of polyclonal and monoclonal antibodies (pages 72-77, 92-97, 128-135 and 141-157 in particular) as well as the types of antigens to which such antibodies can be made including proteins, peptides, and carbohydrates (any of which could qualify as a ligand, depending on the receptor)(pages 153-154 in particular)[claims 46 and 56]. Harlow further teaches that because antibodies may recognize small determinants they may be cross-reactive with similar epitopes on other molecules (page 24, last paragraph in particular) and that epitopes may be formed by linear epitopes within an amino acid sequence or to epitopes which are formed by determinants from different parts of a molecule which are brought together due to conformation of said molecule (page 25, first section in particular). Harlow further teaches the manufacture of Fab and $F(ab')_2$ fragments of monoclonal antibodies (pages 628-631 in particular)[claim 48].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine these references to produce monoclonal antibodies to the NTPPH protein taught by Cardenal. One would have been motivated, with a reasonable expectation of success, to combine these references in order to generate monoclonal antibodies to NTPPH to assist in the identification of regions of the protein involved in the enzyme activity of NTPPH by Harlow's teaching that hybridomas which produce mAbs provide a limitless supply of antibodies which is desirable because even large supplies of antisera (polyclonal) will eventually run out (pages 141-142, section titled "Monoclonal antibodies are powerful immunochemical tools").

Claims 57 and 58 are included because the claims are drawn to a composition but are drafted in a product-by-process manner. However, the antibodies remain the same as, assuming that the instantly disclosed NTPPH-2 has nucleotide pyrophosphohydrolase activity, antibodies which specifically bind the catalytic domains of NTPPH will also bind the catalytic domains of NTPPH-2.

***Conclusion***

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (703) 305-4441. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
December 1, 2003

CHRISTINA CHAN
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TECHNOLOGY CENTER 1600

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